Naval Health Research Center Detachment (Toxicology)

A TYPICAL PATH MODEL OF TRACHEOBRONCHIAL CLEARANCE OF INHALED PARTICLES IN RATS

TOXDET-02-01

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AD NUMBER	DATE	DTIC ACCESSION NOTICE
	29-May-02	

1. REPORT IDENTIFYING INFORMATION

A. ORIGINATING AGENCY

Naval Health Research Center Detachment (Toxicology), WPAFB, OH

B. REPORT TITLE AND/OR NUMBER

A Typical Path Model of Tracheobronchial Clearance of Inhaled Particles in Rats

C. MONITOR REPORT NUMBER

TOXDET-02-01

D. PREPARED UNDER CONTRACT NUMBER

602236N-04124.60163

2. DISTRIBUTION STATEMENT

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PREFACE

This document describes the development and initial validation of a mechanistic, physiologically based mathematical model of aerosol particle clearance by the mucociliary transport system in laboratory rats. The model is meant to complement a specific model of aerosol particle deposition which has been shown to be very accurate yet be run with a personal computer; however the approach can be applied to any model that describes aerosol deposition in the conducting airways in sufficient detail. This work is a portion of an effort to develop mechanistic models of aerosol deposition and clearance that include descriptions of all the particle clearance mechanisms and which are applicable to laboratory animals and humans. Models of this nature are needed to predict aerosol dose from exposure to aerosol threats. The objective is to provide the means to develop accurate health risk assessments for aerosol threats on-site and in real-time using available, advanced aerosol measurement instrumentation.

This work was conducted at the Naval Health Research Center Toxicology Detachment (NHRC/TD) while CAPT Kenneth R. Still, Ph.D., MSC, USN was the Officer-in-Charge. Funding for this effort was granted by the Naval Medical Research and Development Command under work unit #60223-6N.04124.60163. The opinions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Department of Defense, the Department of the Navy, or the Naval Services at large.

Although reference is made to laboratory animals, no animals were used in the investigation described.

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EXECUTIVE SUMMARY

Problem

Understanding of the health risks associated with inhalation of aerosol particles is founded on accurate calculation of dose. Aerosol dose can be described not only in terms of the amount of aerosol deposited in the respiratory tract but also in terms of how long deposited aerosol particles are retained in the respiratory tract or, conversely, how rapidly the particles are cleared. Mechanistic models of aerosol deposition are generally composed of mathematical descriptions of respiratory tract geometry, airflow in that tract, and the physical principles governing particle aerodynamic behavior. Deposition models vary greatly in complexity and predictive accuracy but have limited utility for aerosol dose calculation without corresponding calculation of particle clearance from the respiratory tract. Particles are cleared from the respiratory tract by several mechanisms, one of which is removal of particles deposited in the tracheobronchial airways by transport on mucociliary lining of these airways. At present mechanistic models of tracheobronchial clearance in humans exist but are not fully developed due to insufficient experimental validation which can only be done using a laboratory animal counterpart. A corresponding mechanistic model of tracheobronchial clearance in laboratory animals suitable for this purpose does not exist.

Objective

The objective of the present investigation was to develop a mechanistic model of tracheobronchial clearance of aerosol particles in laboratory rats that could be integrated with proven mechanistic model of aerosol deposition. The model must be physiologically based to facilitate extrapolation between the laboratory animal and human model counterparts. The purpose is to thoroughly validate the animal model through a series of laboratory experiments and to use these data to complete the development of the human model.

Results

A typical path model of tracheobronchial clearance was developed by assuming that particle transport on the mucociliary lining behaved as a continuous flowing stream in which particle number and mass transport was governed by the continuity equation. Mucus transport velocity in a typical airway of given generation of airways was estimated from reported values of tracheal mucus velocity (TMV) by assuming that transport velocity was proportional to airway surface area. A particle clearance model based on typical rat tracheobronchial geometry, an approximate solution of the continuity equation, and these estimated transport velocities was developed and integrated into an existing aerosol deposition model for rats. Theoretical tracheobronchial clearance was calculated for several aerosol exposures reported in the literature and was compared to observe particle clearance and retention reported in these same studies. Model predictions were made for clearance of particles ranging from 0.1 to 4.2 μm in diameter, and overall agreement between predicted and observed retention of initial particle burden agreed within 5%. However there was a tendency to under predict clearance of particles 3.0 μm and larger. Based on these initial findings specific experiments have been designed to verify adjustments to the model.

Conclusion

It appears that treating mucus transport of particles as a continuous flowing stream with regional velocities is a valid approach to modeling tracheobronchial clearance. Certain assumptions regarding mucus thickness and conservation of mucus mass need require examination and systematic experimental validation.

ABSTRACT

A mathematical description of particle clearance from the ciliated conducting airways (tracheobronchial region) of the lungs in rats was developed assuming that particles on the mucus blanket behave as a fluid and adhere to principles of fluid flow described by continuity equation. Effective particle transport velocities for given generations of airways were estimated from reported tracheal transport velocities. Using typical rat airway geometry and estimated particle transport velocities solutions of sets of rate equations for transport from each generation of airways were summed to estimate total particle clearance from the tracheobronchial region of the lung as a function of time. We used a wide range of aerosol particle size distribution data (MMAD ranging from 0.1 to 4.2 mm, and sg from 1 to 2.7) and concentration data from several investigators to predict short term, tracheobronchial clearance (retention) in rats and compared our predictions with their retention measurements. Based on an average of 17 simulations of tracheobronchial clearance the average difference between predicted and observed fractional retention of initial particle burden was 4.9 %, with a tendency toward under prediction of clearance of particles > 3.0 mm.

KEY WORDS
Mucociliary transport, tracheobronchial clearance, inhaled particles, aerosol deposition

INTRODUCTION

There are several defense mechanisms by which deposited particles are removed or cleared from the respiratory tract. Mucociliary clearance is the principal means by which insoluble particles are removed from the conducting, non respiratory airways. These airways, from the trachea to the terminal bronchioles, are lined with ciliated cells and biphasic layer of mucus. Synchronous beating of the cilia propels the mucus toward the tracheal opening where it is subsequently swallowed. Particles captured in or on the mucus also are transported up respiratory tract (Wolff, 1992). Particle removal, in humans, has been considered complete in 24 hours (Albert et. al, 1967); although it has been shown that significant amounts of aerosol may remain in the conducting airways after this time (Smaldone et .al, 1988). Never the less, compared to other mechanisms mucociliary clearance is rapid.

Particle transport rates in the trachea and some of the larger airways have been measured in humans (Chopra et. al, 1979) and several other species (Asmundsson and Kilburn, 1970, Felicetti et. al, 1981, Wolff et. al, 1989). Although it is not possible to measure transport rates in small airways, Yeates and colleagues (1981) demonstrated that tracheal and bronchial transport rates were closely coordinated. Consequently, particle transport rates in smaller airways have been extrapolated from tracheal transport rates to develop mathematical models of mucociliary clearance in humans (Lee et. al, 1979, Cuddihy and Yeh, 1988). Estimated transport velocities for airways beyond the trachea were formulated using the following assumptions. Particle transport velocity in a given airway is inversely proportional to the total surface area of that generation of airways, mucus mass is conserved as it moves up the respiratory tract, mucus coverage in the different generations of airways is uniform, and that there is no net adsorption or secretion of mucus in the airways. We used this approach to develop a model of tracheobronchial clearance in laboratory rats. The typical path tracheobronchial (TPTB) clearance model assumes modified (Wojacik, 1988, Carpenter and Kimmel, 1999) typical path geometry for the rat lung (Schum and Yeh, 1980). This is the same geometry used in the typical path, mechanistic model of aerosol deposition in rodent respiratory tract (Kimmel et. al. 1998, Kimmel et al., 2002) used to predict particle deposition in individual generations of conducting airways upon which the TPTB is dependant.

This report describes model development and provides a comparison between observed and predicted particle retention in rats exposed, by other investigators, to a wide range of particle sizes (0.1 to 4.2 μm, mass median aerodynamic diameter, MMAD).

METHODS

Model Development.

Lee and colleagues (1979) formulated a mechanistic model of tracheobronchial clearance for humans that treats particles on the mucociliary escalator as a fluid and that their concentration is governed by the law of conservation of mass and the continuity equation (1), (Zamir, 2000). The concentration of particles in each airway generation is dependant upon the initial deposition of particles in that generation and the mucus transport rate in that generation.

$$-\vec{V}\cdot\left(\vec{v}\left(\vec{x}\right)\rho\left(\vec{x},t\right)\right)=\frac{\partial\rho\left(\vec{x},t\right)}{\partial t} \qquad (1)$$

where $\rho\left(\vec{x},t\right)$ is particle number density and $\vec{v}(\vec{x})$ is the velocity of particle flow at position $\vec{x}$.

Since only net transport of particles toward the tracheal opening is of concern solution of the one dimensional case is adequate.

$$-\frac{\partial}{\partial x}\left(v(x)\rho(x,t)\right)=\frac{\partial\rho(x,t)}{\partial t} \qquad (2)$$

where $\rho(x,t)$ is the number of particles per unit length of airway at position x and $v(x)$ is the transport rate at this position.

The TPTB model considers clearance from 16 generations of conducting airways which for the present purposes are designated 0 through 15 from the trachea to the terminal bronchioles. If we designate a given branch as α then the next distal generation of branches is α+1 and so forth. An approximate solution of equation (2) can be obtained by averaging it over the length of an airway.

$$\frac{dn_\alpha}{dt}=Z\lambda_{\alpha+1}n_{\alpha+1}-\lambda_\alpha n_\alpha \qquad (3)$$

where $\lambda_\alpha = {}^{v_\alpha}\!/_{l_\alpha}$, v_α is the average transport rate of mucus in generation α, and n_α is the average number of particles in an airway of generation α, and l_α is the average length of an airway in generation α. Z is the factor that takes into account the average number of airways of α+1 that flow into a single airway of generation $\tilde{\alpha}$.

At this point the present model deviates from that developed by Lee and colleagues (1979). They used Weibel's (1963) dichotomously branching lung anatomy where Z uniformly equals two. When applying equation (3) to all branches of a generation, both sides of the equation are multiplied by this factor and the equation reduced leading to an approximation of the continuity equation similar in form to equation (4) below. In this case the <u>average number</u> **N** particles deposited in individual airways of a given generation would be considered in this approximation. However the TPTB assumes that a given particle takes one and only one of many possible paths and considers this typical path representative of all others. Hence transport from one generation of to the next is from a single branch to a single parent airway. Considering a single typical path (or alternately accounting for all branches in a generation) approach equation (4) is obtained. Conservation of mucus mass between generations is factored into the velocity term in λ.

$$\frac{dN_\alpha}{dt} = \lambda_{\alpha+1} N_{\alpha+1} - \lambda_\alpha N_\alpha \qquad (4)$$

where N_α and $N_{\alpha+1}$ differ from **N** in that they denote the <u>total number</u> of particles in all airways in generations α and α+1 respectively.

From Lee and colleagues (1979), the best approach to a solution for equation (4) is to consider it as a family of 16 - α equations, each of which corresponds to initial deposition in a different airway generation. Then for $\beta = 0 - 15$, there is a set of solutions

$$\frac{dN_{\alpha\beta}(t)}{dt} = \lambda_{\alpha+1} N_{\alpha+1,\beta}(t) - \lambda_\alpha N_{\alpha\beta}(t); \qquad (\alpha<\beta) \qquad (5)$$

$$= -\lambda_\beta N_{\beta\ \beta}(t); \qquad (\alpha = \beta)$$

$$= 0; \qquad (\alpha > \beta)$$

with initial conditions

$$N_{\alpha\beta}(0) \qquad = N_\beta^0; \quad (\alpha=\beta) \tag{6}$$

$$= 0; \qquad (\alpha \neq \beta).$$

where $N_{\alpha\beta}$ is the number of particles at any time *t* in generation α due to initial deposition in generation of N_β^0 particles.

For each value of β, equation (5) forms a chain of equations known as the Bateman equations (Bateman, 1910) with a set of solutions.

$$N_{\alpha\beta}(t) \qquad = N_\beta^0 \left\{ \sum_{j=\alpha}^{\beta} \left\{ \prod_{\substack{k=\alpha \\ k\neq J}}^{\beta} (\lambda_k - \lambda_j) \right\}^{-1} e^{-\lambda_j t} \right\} \prod_{m=\alpha+1}^{\beta} \lambda_m; \quad (\alpha < \beta) \tag{7}$$

$$= N_\beta^0 e^{-\lambda_\beta t}; \qquad (\alpha = \beta)$$

$$= 0; \qquad (\alpha > \beta).$$

To obtain the total number of particles in generation α due to deposition in all airway generations, equation (7) is summed over all $\beta \geq \alpha$.

$$N_\alpha(t) = \sum_{\beta=\alpha}^{15} N_{\alpha\beta}(t) \tag{8}$$

If equations (7) and (8) are taken together they give the number of particles present in any generation as a function of time. A less robust alternative solution can be derived by considering transport within a typical airway of each generation. The approximation for transport within generation α becomes

$$\frac{dN_\alpha}{dt} = \lambda_\alpha N_\alpha \qquad (9)$$

There would be similar expressions for each of the other generations a + *i*. Clearance time for particles from a typical airway in a given generation becomes the sum of half the clearance time for that generation plus the clearance times for all preceding generations of airways. The assumption is that clearance of a particle from the midpoint of a typical airway is representative of clearance of the particles distributed across that airway. Solution of this series of chains of equations is simpler however only discrete solutions can be derived which correspond to clearance times from each generation. The solution at intermediate times must be interpolated. With either approach the solution of these expressions which describe concentration of particles in each airway generation as a function of time depends on:

- The initial aerosol deposition pattern.
- The mucus transport rate in each generation.

To determine the transport rates in all airway generations an assumption is made that within an airway generation there is no net adsorption or secretion of mucous. Then by continuity the transport rate of mucous in generation α is given by equation (10).

$$v_\alpha = v_0 A_0 T_0 / Z^\alpha A_\alpha T_\alpha \qquad (10)$$

where $v_0 = \mathrm{TMV}$, A_0 = tracheal surface area, T_0 = tracheal mucous thickness, T_α = mucous thickness in airway α, A_α = surface area of a typical airway in generation α, Z^α = number of airways in generation α.

Although there is evidence that mucous thickness decreases as the airways become smaller (Luchtel, 1978) it is not known whether or not this decrease is systematic or consistent so for a first approximation (which was used in predictions described below) it was assumed that mucous thickness was uniform

(i.e. $T_0 = T_\alpha$). Thus equation (10) becomes equation (11).

$$v_a = v_0 A_0 / Z^\alpha A_\alpha \tag{11}$$

The tracheal mucociliary velocity (TMV) used in the model (1.24 mm/min) was derived from a combination of allometric relationships (Wolff, 1992):

- TMV = 2.98(body weight)$^{0.4}$
- TMV = 0.01(tracheal length)$^{2.22}$
- TMV = 0.17(tracheal diameter)$^{1.5}$
- TMV = 0.80(tracheal surface area)$^{0.55}$.

This TMV agreed with those reported for rats byseveral investigators (Giordano and Morrow, 1972, Patrick and Stirling, 1977, Felicetti et. al, 1981). Mucociliary velocities in the remaining airways were estimated by assuming that the TMV diminished by a factor directly proportional to the relative difference between tracheal surface area and the surface area of typical airway in an a given generation, and inversely proportional to the total surface area of an airway generation. These initial estimates of transport velocity in the smaller airways also were adjusted to preserve mass transport of mucus from one generation of airways to the next. It was assumed that there was no net adsorption or secretion of mucus in the airways. The relevant airway geometry, velocities, and clearance times (defined as time for a particle to travel from the midpoint of the airway to the tracheal opening) are shown in Table 1.

We recently developed a typical path model of aerosol deposition (TPAD) model that predicts particle deposition in the extrathoracic (ET), tracheobronchial (TB), and pulmonary regions of the lungs of laboratory rodents (rats or guinea pigs). Total particle deposition probability is calculated as the sum of the probabilities of deposition by aerodynamic (inertial impaction, sedimentation), and thermodynamic (diffusion) mechanisms. Where the probabilities for deposition by these mechanisms are calculated as follows:

1. Probability of impaction (equation 12 - all flow regimes).

$$P_i = 1 - \frac{2}{\pi}\cos^{-1}(\theta \cdot St) + \frac{1}{\pi}\sin\left(2\cos^{-1}(\theta \cdot St)\right) \tag{12}$$

where: St = Stokes number and θ = branch angle. when $\theta \cdot St \geq 1, P_i = 1$.

2. Probability of sedimentation (equation 13 - all flow regimes).

$$P_s = 1 - \exp\left(-4gC\rho_p r^2 L\cos\varphi / 9\pi\mu R\bar{v}\right) \quad (13)$$

where: C = Cunningham slip correction factor, ρ_p = particle density, r = particle radius, μ = viscosity, R = radius of the airway, L= airway length,

$\bar{v}$ = mean velocity, g = gravitational constant, and φ = gravity angle.

During breath pause $L/\bar{v}$ is replaced by t which in this case is pause time.

3. Probability of diffusion (thermodynamic – equations 14, 15, and 16)
(Laminar flow)

$$P_d^l = 1 - 0.818e^{-7.315x} - 0.0976e^{-44.61x} - 0.032e^{-114x} - 0.050e^{-79.31x} \quad (14)$$

where: x= $LD/2R^2\bar{v}$, and D = Diffusion coefficient for particles

(Turbulent flow)

$$P_d^t = \frac{2\sqrt{Dt}}{R}\left(1 - \frac{2\sqrt{Dt}}{9R} + \ldots\right) = 2.828\sqrt{x}\left(1 - 0.314\sqrt{x}\ldots\right) \quad (15)$$

where: t = time for flow through airway = $L\bar{v}$.

(Breath pause)

$$P_d^p = 1 - \exp\left(-5.784KTCt / 6\pi\mu R^2\right) \quad (16)$$

where: K = Boltzmann constant, T = temperature Kelvin, and t = pause time.

RESULTS

As noted above the TPTB clearance model is dependent upon an accurate estimation of particle deposition in each generation of airways. Thus a review of TPAD performance is in order. Figures 1 -3 show predicted regional deposition curve compared to reported particle deposition of various size particles from studies by other investigators. Regression analysis of predicted versus reported particle deposition (Figures 4-6) show good agreement between TPAD predictions and observed deposition.

Theoretical retention of monodisperse aerosols with MMADs ranging from 0.3 to 4.5 μm are

shown in Figure 7. We also have used TPAD and TPTB to simulate short term (assumed to be mainly mucociliary) clearance in rats after exposure to a variety of particle size distributions with MMADs ranging from 0.1 to 4.2 μm and geometric standard deviations (σgs) ranging from 1.1 to 2.7. We compared predicted with observed fractional initial lung or fractional initial body burden from these studies. (TABLE 2). Average agreement between predicted and observed particle retention was 4.9 %, with a tendency to under predict clearance (over predict retention) for particles ≥ 3.0 μm. Although an agreement of 4.9 % between simulated and observed clearance is reasonably good (Figure 8) it must be interpreted in the perspective that theoretical maximum fractional mucociliary clearance of particles ranging from 0.3 to 4.5 μ m was 14.7 to 45.9 % respectively.

DISCUSSION

The TPTB clearance model apparently gives a reasonable estimate of mucociliary clearance of particles from the conducting airways of rats. Theoretically clearance from the TB region of the lungs of rats is complete after 26.6 hours which is in agreement with the literature (Iravani and van As, 1971). Lee and colleagues observed three phases of tracheobronchial clearance in humans; an initial slow phase lasting about 30 minutes, a rapid phase lasting 1 to 2 hours and a slow phase lasting until most particles were cleared in 6 hours. They attributed the initial slow phase to the time delay to accumulation of particles in the main bronchi prior to clearance. The rapid phase of clearance was attributed to the relatively higher mucus transport velocities in the larger airways and the small distances traversed from the large airways to the trachea. The final slow phase was attributed to the relatively slower mucus transport velocities of the smaller airways and the larger distances traveled from the small airways to the trachea. The TPTB rat model also predicts multi-phasic clearance, consisting of at least an initial rapid component and a slower component reflecting relatively lower mucus velocities in the smaller airways. The apparent lack of an initial slow phase component of mucociliary clearance in the TPTB rodent model may well reflect the fundamental difference between symmetric biopodial structure of human airway anatomy and the asymmetric, monopodial structure of rodent airway anatomy.

There was an average 4.9 % difference between predicted and observed fractional particle retention taken from data collected at times ranging from 6 to 30 hours (average 20.6 hrs) post exposure. Their also was a tendency for the model to under predict clearance of particles 3.0 μm and larger. The

present model treats clearance from the ET region as immediate and does not account for clearance from the P region which may occur in this time frame by particle laden macrophages migrating to the mucociliary escalator and being cleared along with particles deposited directly on the mucus blanket. Although agreement between model predictions and experimental findings within 5% is remarkable this figure must be considered in proper perspective. Given that theoretical maximum fractional clearance via the mucociliary escalator ranges from 18 to 49% for 0.3 to 4.5 μm particles respectively the 4.9 % difference between observed and predicted retention may actually be between 10 and 27.2%. Over and under estimates of fractional deposition in the ET and P regions also must be considered in these observations. The estimated effective velocities used in the model require further adjustment to account for known differences in coverage and thickness between the proximal and distal airways. Despite these reservations it appears that this simple approach toward simulating the complexities of mucociliary particle clearance may prove useful in the development of physiologically based mathematical models of aerosol deposition and clearance, which are useful for dosimetry calculations and risk assessments. Unfortunately there are very few existing data bases which can be used to judge model performance and most of the existing data involve observations at time frames nearing the end of theoretical clearance of particles deposited directly in the conducting airways. Additional experiments are currently underway to fill in missing information about early mucociliary clearance and how it relates, temporally and quantitatively, to short term clearance from the ET region as well as early clearance from the P region.

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Table 1. Airway geometry, effective velocities, & clearance times

Gen.	No.	Diameter (cm)	Length (cm)	Velocity (mm/min)	Clearance Time (hrs)*
1	1	0.292	2.42	1.2414	0.162
2	2	0.2491	0.6456	0.6187	0.412
3	3	0.2259	0.3612	0.1892	0.658
4	5	0.1743	0.1589	0.0857	0.972
5	8	0.1400	0.1878	0.0305	1.640
6	14	0.1151	0.1056	0.0263	2.488
7	23	0.1056	0.1029	0.0130	3.484
8	38	0.0962	0.1174	0.0115	4.994
9	65	0.0816	0.0894	0.0104	6.562
10	109	0.0747	0.0822	0.0077	8.174
11	184	0.0670	0.0867	0.0064	10.192
12	309	0.0601	0.0659	0.0060	12.223
13	521	0.0498	0.6773	0.0041	14.491
14	877	0.0421	0.0542	0.0035	17.132
15	1477	0.0309	0.0497	0.0023	20.156
16	2487	0.0172	0.0316	0.0006	26.661

* Time for particle to move from center of airway to tracheal opening

TABLE 2. Observed versus Predicted Particle Retention.

Aerosol size (mmad,σg)	Time post exposure (hrs)	Observed	Predicted	Observed minus Predicted	Reference
		Fraction of ILB or IBB retained in lung			
0.1 μm, 1.0	12	0.84	0.82	0.02	Wolff et. al
0.1 μm, 1.0	24	0.71	0.74	- 0.03	Wolff et. al
0.61 μm, 1.2	20	0.95	0.89	0.06	Rabbe et. al (1974)
0.67 μm, 1.0	24	0.88	0.83	0.05	Snipes et. al (1977)
1.14 μm, 1.2	20	0.89	0.82	0.07	Rabbe et. al (1974)
1.38 μm, 1.0	24	0.82	0.78	0.04	Snipes et. al (1977)
1.39 μm, 2.74	6	0.33	0.30	0.03	Benson et. al
1.39 μm, 2.74	24	0.30	0.27	0.03	Benson et. al
1.4 μm, 1.3	6	0.93	0.87	0.06	Newton & Pfledderer
1.4 μm, 1.3	20	0.80	0.78	0.02	Newton & Pfledderer
1.4 μm, 1.3	30	0.74	0.74	0.00	Newton & Pfledderer
2.19 μm, 1.2	20	0.82	0.89	-0.07	Rabbe et. al (1974)
2.79 μm, 1.0	24	0.60	0.65	-0.05	Snipes et. al (1977)
3.0 μm, 1.0	24	0.32	0.30	0.02	Snipes et. al (1984)
3.15 μm,1.2	20	0.51	0.69	-0.18	Rabbe et. al (1974)
4.18 μm, 1.2	20	0.53	0.48	0.05	Rabbe et. al (1988)
9.0 μm, 1.0	24	0.001	0.000	n.d.	Snipes et. al (1984)
15.0 μm, 1.0	24	0.001	0.000	n.d.	Snipes et. al (1984)

ILB = initial lung burden (TB+P), IBB = initial body burden (ET+TB+P)

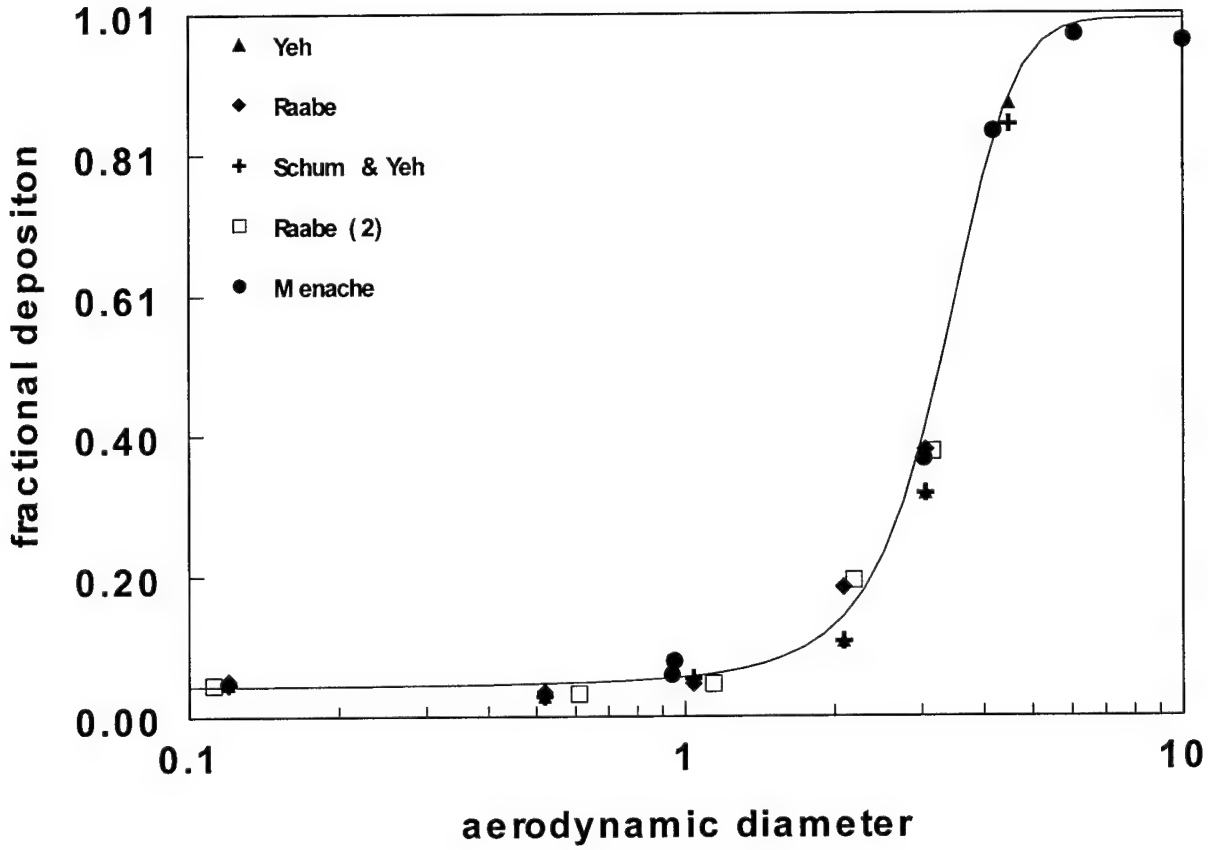

Figure 1. Extrathoracic Aerosol Deposition.

TPAD predictions = solid line

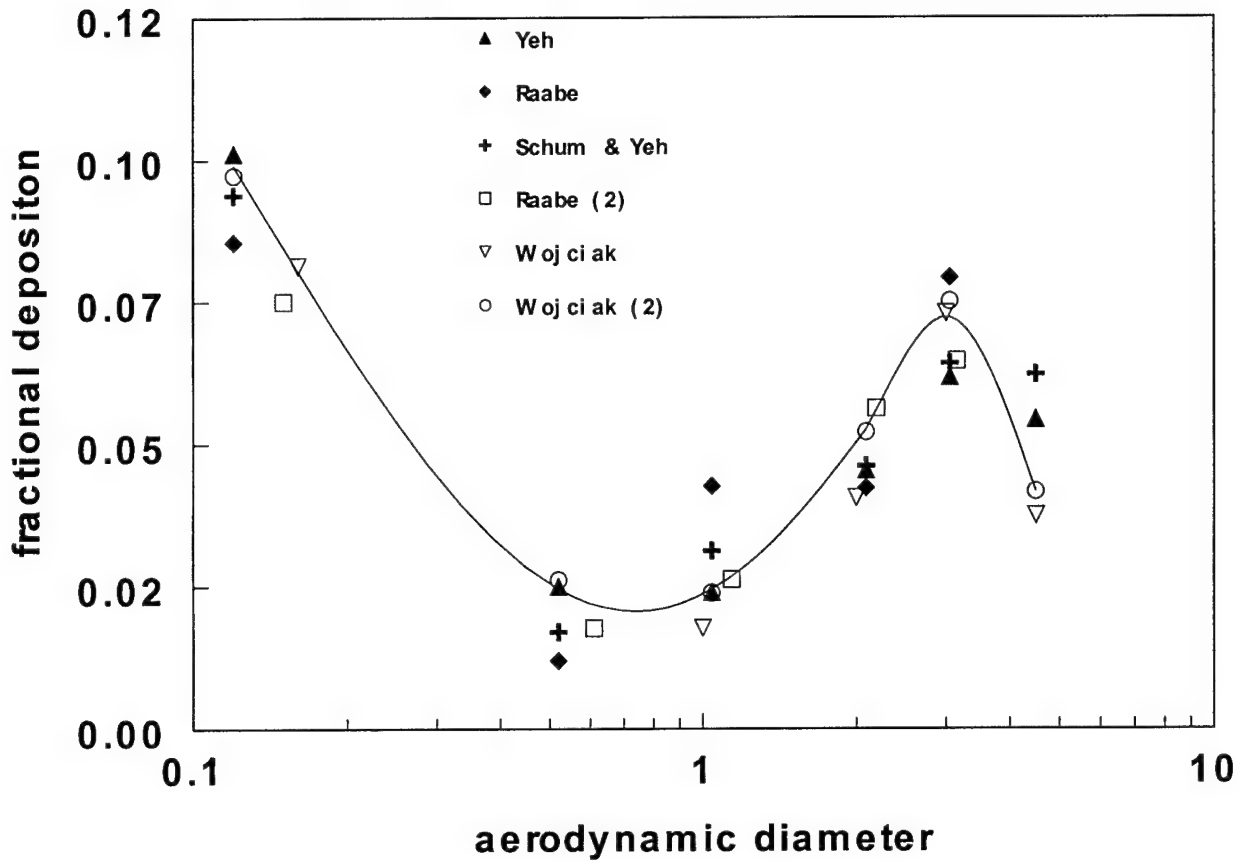

Figure 2. Tracheobronchial Aerosol Deposition.

TPAD predictions = solid line

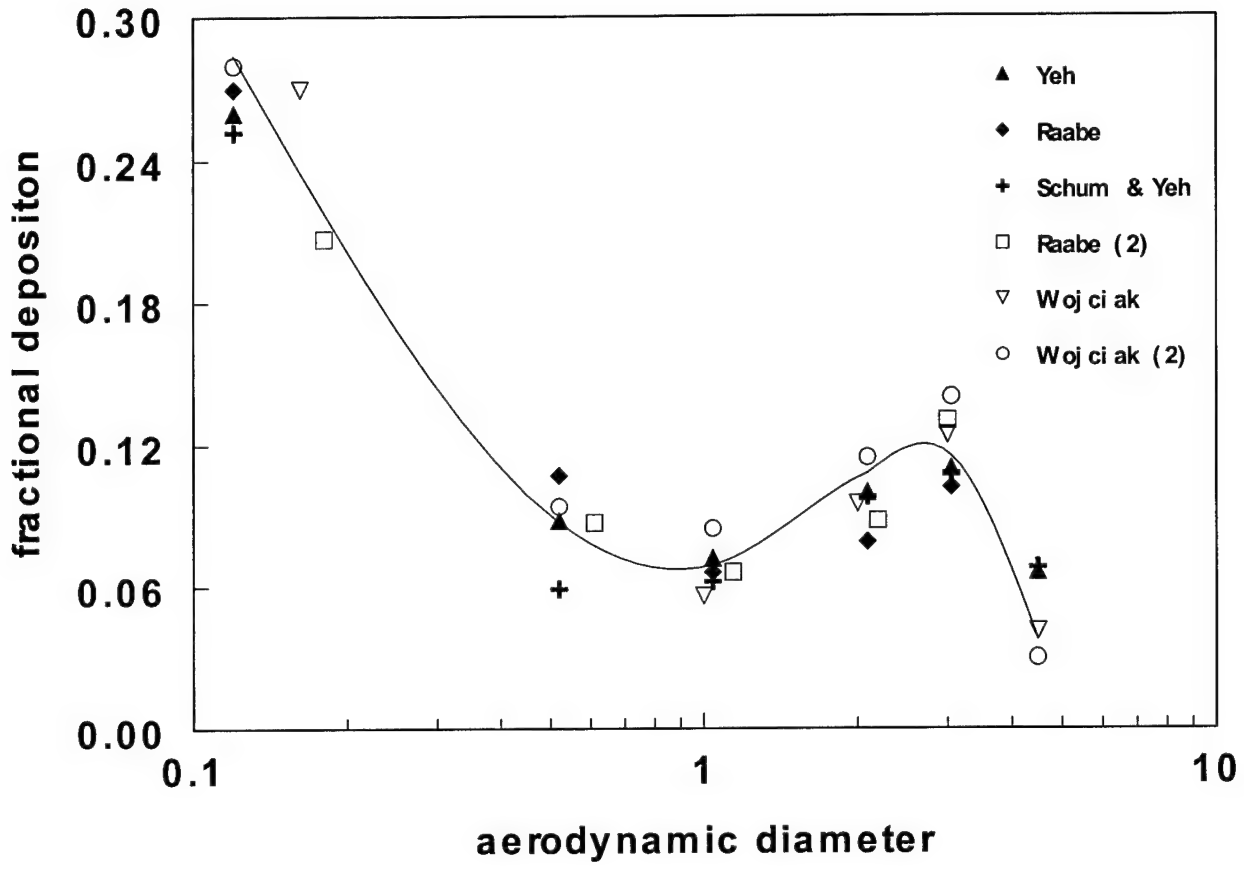

Figure 3. Pulmonary Aerosol Deposition

TPAD predictions = solid line

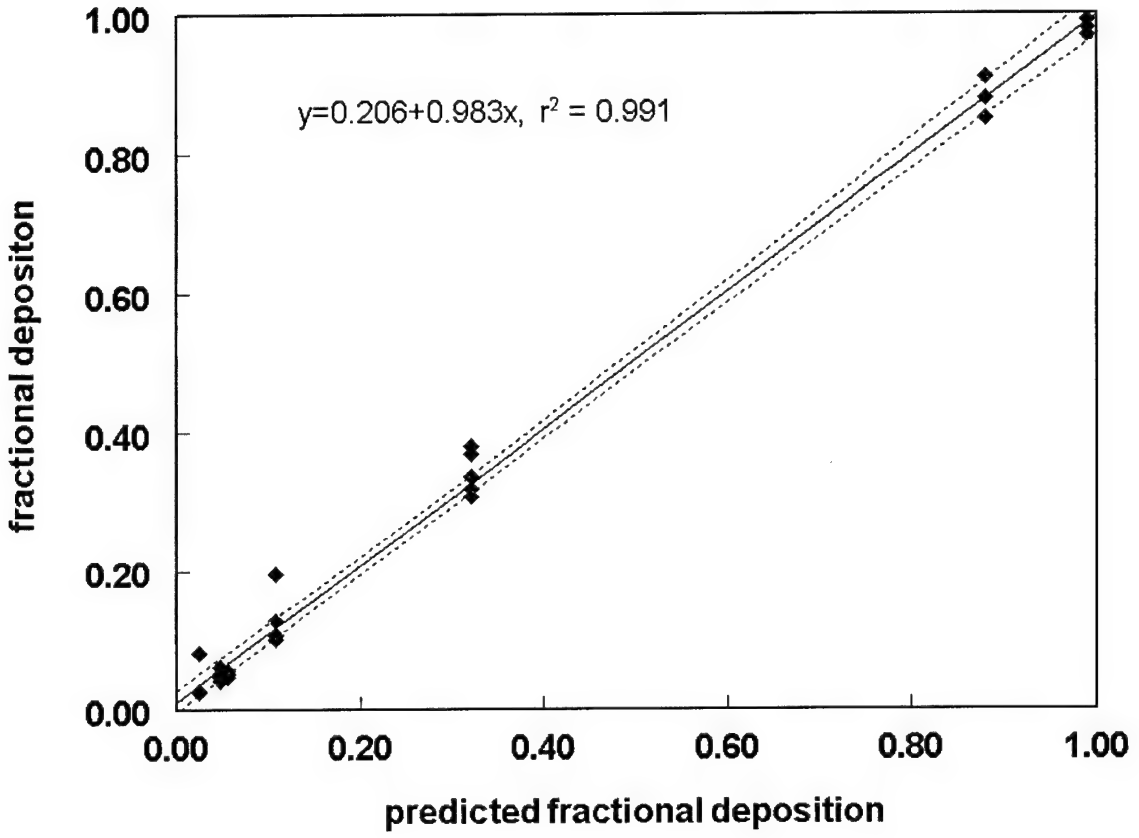

Figure 4. Observed versus Predicted Extrathoracic Region Aerosol Deposition.

Dashed lines are 99 % confidence limits.

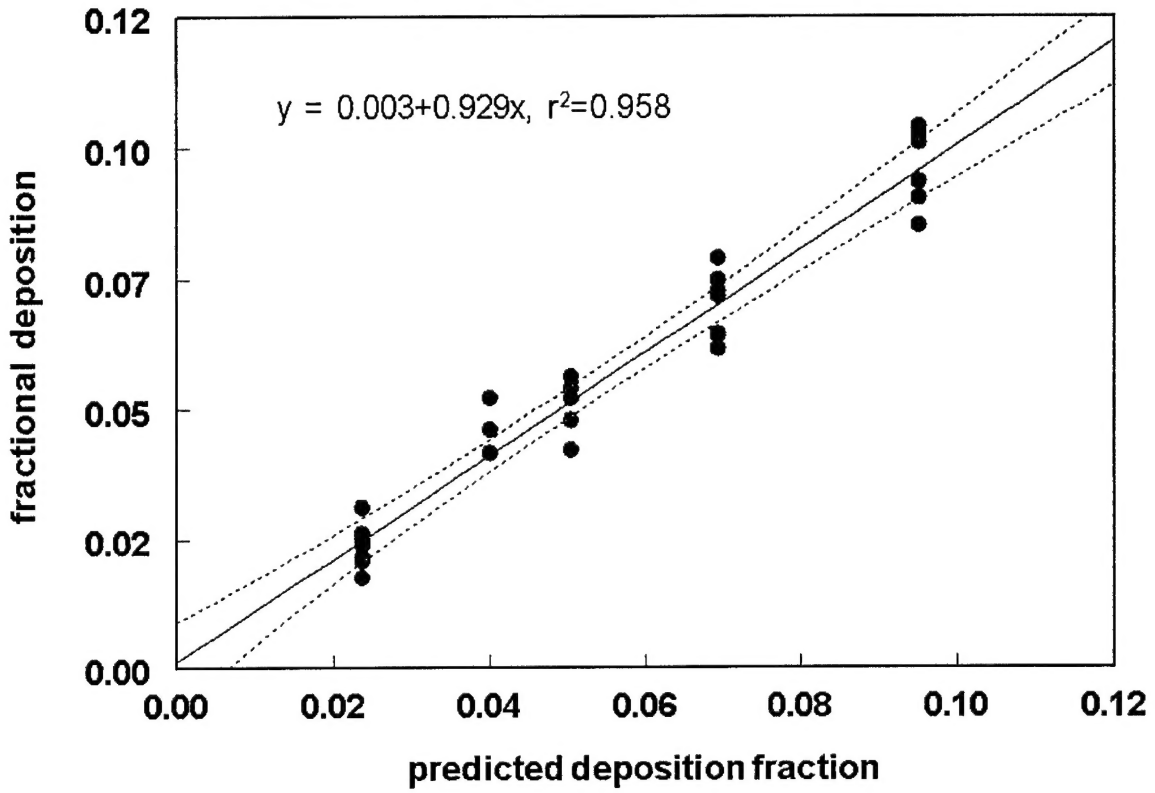

Figure 5. Observed versus Predicted Tracheobronchial Region Aerosol Deposition

Dashed lines are 99% confidence limits.

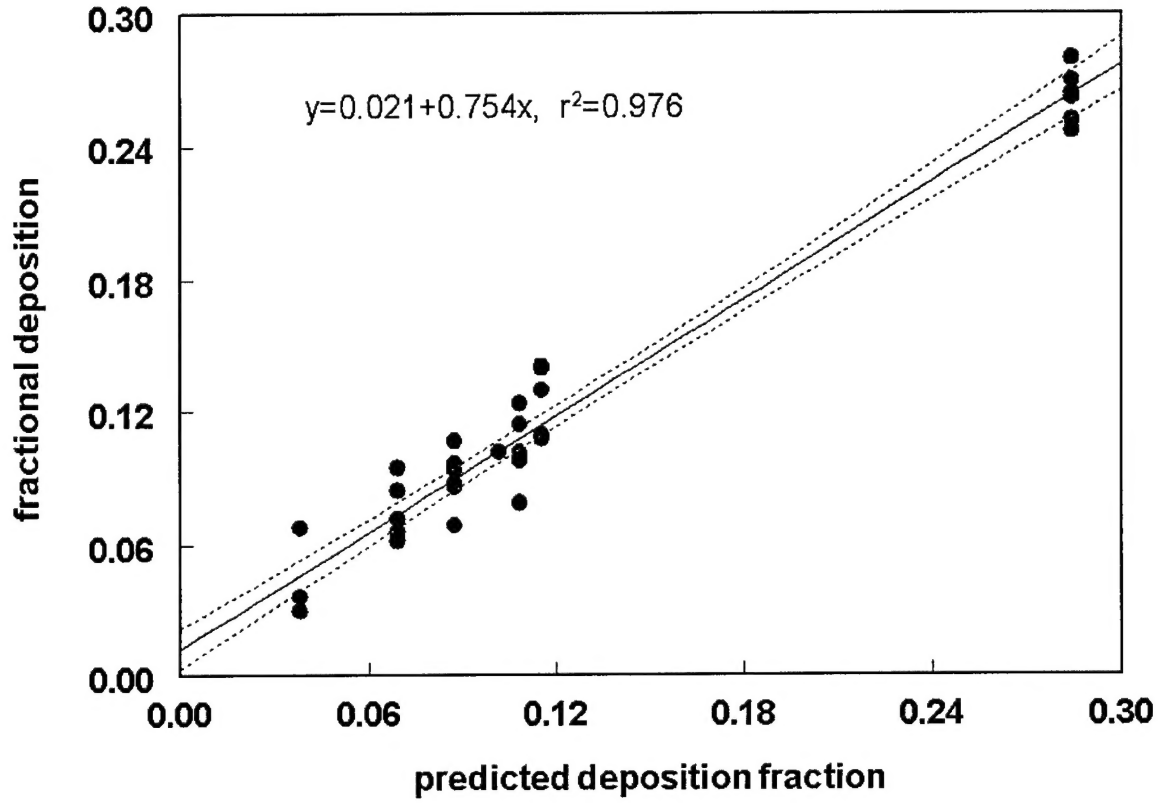

Figure 6. Observed versus Predicted Pulmonary Region Aerosol Deposition

Dashed lines are 99% confidence limits.

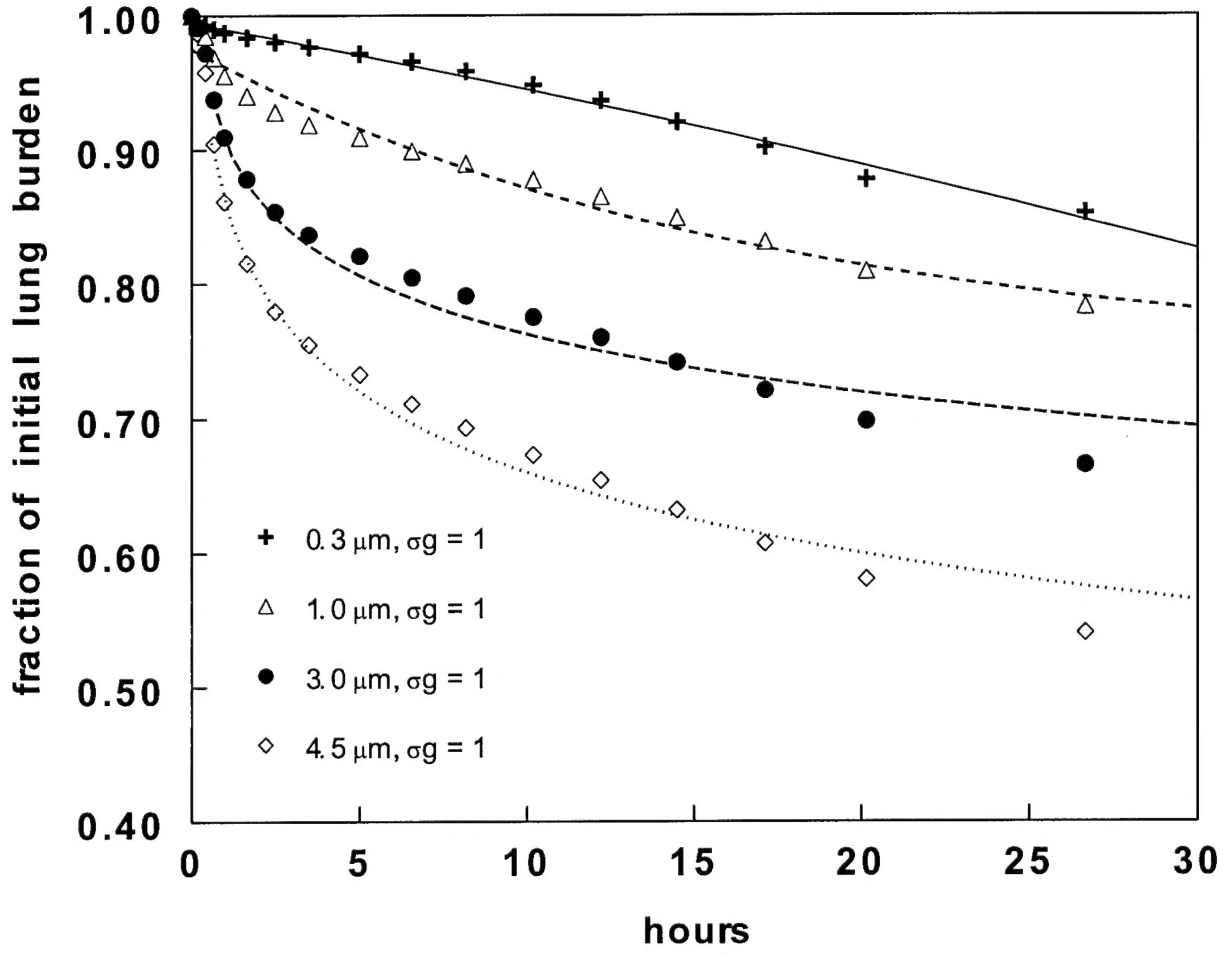

Figure 7. Theoretical retention of monodisperse aerosols.

Symbols are TPTB predictions

Lines are best 2 component exponential or logarithmic fit of data

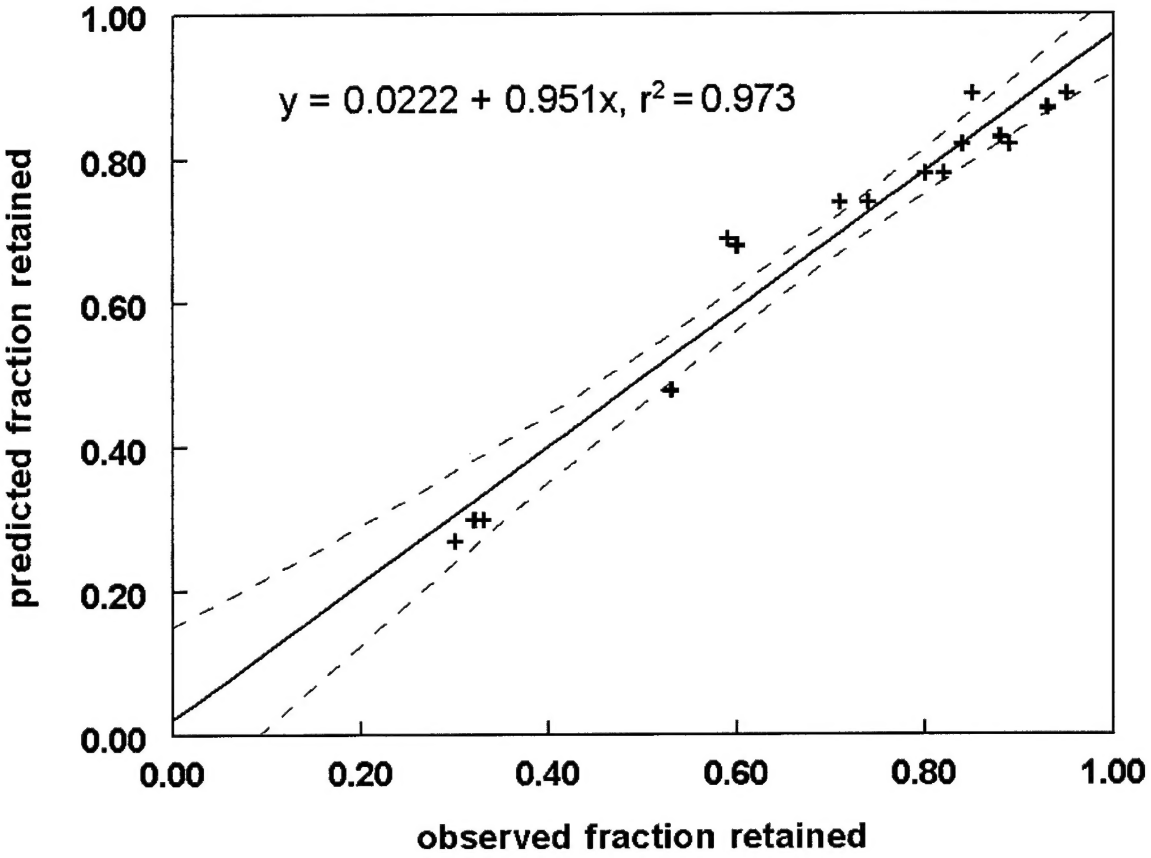

Figure 8. Observed versus Predicted Aerosol Retention

Dashed lines are 99% confidence limits.